Remarks

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Status of the Claims

Upon entry of the foregoing amendments, claims 1-11, 19, 21 and 23-28 are pending in the application, with 1, 19 and 21 being the independent claims. In the Office Action dated March 2, 2004, page 1, the Examiner stated that claims 15-17 were also under consideration. However, Applicants bring to the Examiner's attention that claims 15-17 were canceled in the Supplemental Amendment and Reply Under 37 C.F.R. 1.111 faxed to the Examiner on August 8, 2003.

Claim 13 has been canceled. Claims 12, 14-18, 20 and 22 were previously canceled. In the Office Action dated March 2, 2004, page 2, the Examiner stated that claims 12, 14, 18 and 20 were previously canceled. However, Applicants bring to the Examiner's attention that additionally, claims 15-17 and 22 were previously canceled.

Claims 1, 2, 4, 10, 11, 19, 21 and 25 have been amended. Support for these amendments can be found throughout the specification as filed. For example, support for amended claims 1, 19 and 21 can be found on page 8, lines 13-14; support for amended claims 2 and 4 can be found on page 12, lines 8-10 and 21-22; and support for amended claim 11 can be found on page 14, line 29. No new matter has been introduced by the amendments. Applicants respectfully request entry of these amendments.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 4, 7, 10, 11, 21, 23-28 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 2 has been amended to recite "wherein at least one cancer cell is a terminal cell that is a fragile, large cancer cell compared to white blood cells from the patient, with a large nucleus high nucleus to cytoplasm ratio when compared to white blood cells from the patient."

Claim 4 has been amended to recite "is a terminal cell that is a fragile, large cancer cell compared to white blood cells from the patient, and is without a nucleus."

The Examiner stated "[i]t is unclear how a 'fragile large cancer cell' has the quality of being a 'fragile large cancer cell' rather than a 'large cancer cell.'" The Examiner's rejection is unclear. The fragility of the isolated cancer cell is described in the specification on page 2, paragraph 3. Applicants request that this rejection be clarified, or that the Examiner withdraw this rejection.

The Examiner stated that "[t]he term 'late stage' is a relative term" and "[i]t is unclear how to determine the difference between the 'late stage' dying cell of claims [*sic*] 7 and a nucleated terminal cell which [is] dying." Applicants submit that the term "late stage" is definite in that it is qualified by the phrase "and is breaking into pieces." Thus, the terminal cells which are late stage dying cells and breaking into pieces are distinctly claimed. "Late stage" cells in the terminal pathway are also defined in the specification on page 13, lines 12-18. Thus, the claims particularly point out and distinctly claim the subject matter of the invention.

Claim 10 has been amended to delete the term "small."

Claim 11 has been amended to recite "wherein three to 100 isolated cancer cells are in the form of a microtumor."

Claim 21 has been amended to recite "(e) comparing the number of said first isolated cancer cells to the number of said second isolated cancer cells, or comparing the class of said first isolated cancer cells to the class of said second isolated cancer cells."

Claim 25 has been amended to delete the phrase "for a period of time."

In view of the above amendments and remarks, it is respectfully requested that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

A. The rejection of claims 1-11, 13, 15-17, 19, 21 and 23-28 under 35 U.S.C. § 112, first paragraph, must be withdrawn.

Claims 1-11, 13, 15-17, 19, 21 and 23-28 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Specifically, the Examiner alleges that the specification, while being enabling for circulating cancer cells in the blood which are epithelial, does not reasonable provide enablement for two additional classes of cells: (1) circulating non-epithelial cancer cells, and (2) circulating epithelial cells which are not in the blood. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 2-11 and 13 are ultimately dependent on independent claim 1. Claim 19 is an independent claim. Claims 23-28 ultimately depend from independent claim 21. Applicants bring to the Examiner's attention that claims 15-17 were previously canceled.

With regards to the first class of cells, solely to expedite prosecution, claims 1, 19 and 21 have been amended to recite "circulating *epithelial* cancer cells." Claim 13 has been canceled.

With regards to the second class of cells, the Examiner's attention is directed to independent claims 1, 19 and 21,which are directed to cancer cells *in a sample of blood.*

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

B. The rejection of claim 26 under 35 U.S.C. § 112, first paragraph, must be withdrawn.

Claim 26 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Specifically, the Examiner alleges that the specification does not reasonably provide enablement for the medical procedure of gene therapy. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 26 is dependent on claim 21. Claim 21 is directed to a method of determining the efficacy of a medical procedure for treatment of cancer in a patient. Claim 21 is not directed to the medical procedure itself, only in determining the *efficacy* of a medical procedure. Claim 26 lists gene therapy as one possible medical procedure for which the efficacy could be determined. In the Office Action of March 2, 2004, page 4, the Examiner noted that the specification is enabling for methods of treatment consisting of surgery, radiation, hormone therapy and therapeutic agent administration. The *method of determining efficacy* for gene therapy would be the same method used to determine efficacy of surgery, radiation, hormone therapy and therapeutic agent administration. Thus, the method of the invention as claimed is enabled.

In view of the above, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

A. The rejection under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rimm *et al.* in view of LaVia *et al.*, Maggi *et al.*, and Pavone *et al.* must be withdrawn.

Claims 1, 8, 11, 13, 15-17, 21 and 23-28 2 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rimm *et al.* (U.S. Patent No. 6,197,523) in view of LaVia *et al.* (*Principles of Pathobiology*, 213 (1975)), Maggi *et al.* (*Cango 16*:169-188 (1963)), and Pavone *et al.* (*Clinical Ostetrica E. Ginecologica 65*: 475-80 (1963)). Applicants respectfully traverse.

Claims 1 and 21 are independent claims. Claims 8, 11 and 13 depend directly from claim 1. Claims 23-28 depend either directly or indirectly from claim 21. Applicants bring to the Examiner's attention that claims 15-17 were previously canceled.

Claim 1 is directed to a method of classifying epithelial cancer cells in a sample of blood from a patient with cancer or a patient suspected of having cancer, said method comprising isolating circulating epithelial cancer cells from said sample and classifying said isolated cancer cells as terminal cells or proliferative cells by cytological and morphological analyses using fluorescence microscopy.

To establish a *prima facie* case of obviousness, the cited document(s) must teach or suggest each and every element of the claimed invention. Additionally, there must be some suggestion or motivation, either in the prior art itself on in the knowledge generally

available to one of ordinary skill in the art, to modify the prior art or combine the teachings of the prior art in the matter posited by the Examiner. MPEP § 2143.

Applicants submit that the cited documents provide no suggestion or motivation to combine each and every element of the claims into an invention. The claims require the use of fluorescence microscopy for the classification of cancer cells in a sample of blood from a patient with cancer or a patient suspected of having cancer.

Rimm discloses the identification of an epithelial cell by using an E-cadherin/Cy3 marker and confirms the presence of cells with abnormal morphology with an acridine orange stain. According to Rimm, cells that contain both the E-cadherin/Cy3 marker and the acridine orange stain "alerts the cytopathologist to the strong likelihood of a cancerous tumor." (Col. 10, lines 4-10.) Rimm does not disclose the *classification* of cancer cells based on cytological and morphological analyses. Rimm does not even distinguish between cancer cells in the terminal pathway versus the proliferative pathway.

Likewise, neither the Pavone nor the Maggi abstracts disclose the classification of cancer cells based on cytological and morphological analyses of isolated cells. Neither Pavone nor Maggi distinguish between isolated cancer cells in the terminal pathway versus the proliferative pathway.

LaVia discloses that most individual neoplastic cells that enter the bloodstream die without forming a new nidus of malignant disease. LaVia does not describe the use of, or provide a motivation to use, a method to classify cancer cells in a sample of blood from a patient with cancer. LaVia does not describe the use of, or provide a motivation to use, fluorescence microscopy to perform cytological and morphological analyses to

classify isolated cancer cells. Neither Rimm, Pavone nor Maggi suggest or provide a motivation to combine the observation of LaVia with a method to classify cancer cells in a sample of blood from a patient with cancer. Neither Rimm, Pavone nor Maggi suggest or provide a motivation to combine the observation of LaVia with the use of fluorescence microscopy. Thus, neither Rimm, Pavone, Maggi or LaVia provide any suggestion or motivation to modify or combine their teachings to provide a method of the claimed invention. The Examiner has failed to establish a *prima facie* case of obviousness of the presently claimed invention and the Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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